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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,305	12/06/2001	Charles E. Prussak	ST-UCSD3140	1335

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/006,305	PRUSSAK ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/17/08, 05/09/08, 10/13/08, 01/09/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,8,11,12,14,16-21,23-29,32-41,43-51,62-68 and 76-79* is/are pending in the application.

4a) Of the above claim(s) *14,16-21,23-26,43-51 and 62-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,8,11,12,27-29,32-41,68 and 76-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/13/2008, 10/14/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. It is noted that the claims have been amended several times to clarify the claimed invention and the status of the claims themselves, since the last non-final Office Action, mailed 08/24/2007.

This Office Action is based upon the claims submitted on 10/13/2008.

Claims 1, 5-7, 9-10, 13, 15, 22, 30-31, 42, 52-61 and 69-75 have been canceled previously

Claims 2-4, 8, 11-12, 14, 16-21, 23-29, 32-41, 43-51, 62-68 and 76-79 are pending.

Claims 2-4, 8, 11-12, 27-29, 32-41, 68 and 76-79 are being acted upon as the elected invention.

Applicant's election without traverse of Group I for examination, and the species wherein Domains I, II and III are fragments of CD154 (i.e. CD40L), while Domain IV comprised a fragment of human TNFα has been acknowledged.

As indicated previously,
for examination purposes, the elected claims 2-4, 8, 11-12, 27-29, 32-41 and 68-75 are being examined to the extent they read on the elected species wherein Domains I, II and III are fragments of CD154 (i.e. CD40L), while Domain IV comprised a fragment of human TNFα.

Claims 14, 16-21, 23-26, 43-51 and 62-67 have been withdrawn from consideration as being drawn to the nonelected inventions and/or species.

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 2-4, 8, 11-12, 27-29, 32-41, 68 and 76-79 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.
The specification as originally filed does not provide support for the invention as now claimed: "the Domain III comprises a CD154 fragment lacking a metalloproteinase cleavage site present in wild-type CD154" (see claim 2(a)).

Applicant's amendment, filed 01/17/2008, directs support to paragraphs [0007], [0009] and [0078] of the instant specification for the newly added claims.

However, the recitation of "lacking a metalloproteinase cleavage site" and "wild-type" is described in the context of TNF and not in the context of CD154, as currently claimed.

Therefore, the recitation of "lacking a metalloproteinase cleavage site" and "wild-type" in the context of CD154 changes the scope of the instant application and, in turn, is deemed to be new matter.

It does not appear that the instant specification provide sufficient written description for the recitation of "lacking a metalloproteinase cleavage site" and "wild-type" in the context of CD154.

The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitation" as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above.
See MPEP 714.02 and 2163.06

4. This is a 35 U.S.C § 112, first paragraph, "written description" (and not new matter).

Claims 2-4, 8, 11-12, 27-29, 32-41, 68 and 76-79 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

The specification as originally filed does not provide support for the invention as now claimed:
"a CD154 fragment lacking a metalloproteinase cleavage site present in wild-type CD154" and
"than are native TNFα and TNFα lacking a mmmp cleavage site between Val77 and Pro88 of native TNFα".

With respect to "a CD154 fragment lacking a metalloproteinase cleavage site present in wild-type CD154",
the specification appears to describe CD154 fragments in terms of CD154 domains and not fragments per se.

Given that the current recitation of "fragments" can read on fragments less than a CD154 domain, including a single amino acid,

the instant recitation of "Domain III comprises" reads on a wide range of structural variation that differs from CD154 or a CD154 domain.

Further, the instant recitation of "Domain III comprises" does not require necessary functional characteristics coupled with a known or disclosed correlation between function and structure.

With respect to the recitation of "than are native TNFα and TNFα lacking a mmmp cleavage site between Val77 and Pro88 of native TNFα",

the specification does not appear to provide a clear description of necessary functional characteristics coupled with a known or disclosed correlation between function and structure of native TNFα.

There is insufficient written description as to whether the recitation of "native TNFα" describes a particular species of native TNFα (e.g., human, mouse), TNFα before or after processing or transmembrane or soluble TNFα.

Further, in the absence of a reference sequence (e.g. SEQ ID NO.), there is insufficient description of "a mmmp cleavage site between Val77 and Pro88 of native TNFα".

For example, Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Applicant was not in possession of the claimed genera of "CD154 fragments" or "native TNFα" as elements of the claimed nucleic acid molecules in the absence of providing sufficient structural and functional characteristics of the genera of such "CD154 fragments" or "native TNFα" encompassed by the instant claim language, coupled with a known or disclosed correlation between function and structure.

The instant application has not provided a sufficient description showing possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genera of "CD154 fragments" or "native TNFα" broadly encompassed by the claimed invention.

Further, the Court has interpreted 35 U.S.C. §112, first paragraph, to require the patent specification to "describe the claimed invention so that one skilled in the art can recognize what is claimed. Enzo Biochem, Inc. v. Gen-Probe Inc, 63 USPQ2d 1609 and 1618 (Fed. Cir. 2002). In evaluating whether a patentee has fulfilled this requirement, our standard is that the patent's "disclosure must allow one skilled in the art 'to visualize or recognize the identity of' the subject matter purportedly described." Id. (quoting Regents of Univ. of Cal. v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed Cir. 1997)).

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus.

It is not sufficient to define a genus without sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics.

In the absence of sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, the claimed invention is not described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

The problem here is that the instant specification fails to provide a disclosure of which "CD154 fragments" or "native TNFα molecules" are required for the claimed nucleic acid molecules, broadly encompassed by the claimed invention.

A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that exhibit this functional property.

Therefore, there is insufficient written description for genera of "B7 antigens", broadly encompassed by the claimed invention at the time the invention was made and as disclosed in the specification as filed under the written description provision of 35 USC 112, first paragraph.

Applicant has been reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

5. Upon reconsideration of applicant's amended claims, arguments in conjunction with the Prussak Declaration, filed , that the Cantwell Abstract (and Poster Sesssion) that the refernced chimera did comprise a CD154 cleavage site,

the previous rejection under 35 U.S.C. § 102(a) as being anticipated by Cantwell et al. (Blood 11 (Part 1): page 423a, November 16, 2001 (see Abstract) has been withdrawn.

6. Claims 2-4, 8, 11-12, 27-29, 32-41, 68 and 76-79 are rejected under 35 U.S.C. §. 103(a) as being unpatentable over Kipps et al. (U.S. Patent No. 7,070,771) AND/OR Kipps et al. (WO 98/26061) in view of Mueller et al. (J. Biol. Chem.274: 1999) (1449) and Kornbluth (US 2005/0158831 A1) essentially for the reasons of record.

Applicant's arguments in conjunction with the Foon Declaration, filed 05/21/2007, as well as with the Prussak 132 Declaration, filed 10/05/2006 and KSR, have been fully considered but have not been convincing essentially for the reasons of record and reiterated herein for applicant's convenience.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Further, while applicant asserts that the principal focus of Kornbluth et al. is on the creation of soluble fusion proteins and acknowledges that Kornbluth et al. does teach changing the solubility of fusion protein via mutagenesis of the CD1564 cleavage site,

applicant argues that nothing in Kornbluth et al. suggests the removal of the mmp cleavage site from the CD154 would prevent release of an otherwise soluble CD154 fusion protein.

In contrast to applicant's arguments that Kornbluth et al.'s teachings are limited by their explicit terms to CD154-SPD fusion proteins and that there was a daunting task of identifying and eliminating an array of mmp cleavage sites from different chimeric species,

the teachings of Kornbluth are not is isolation and but rather are consistent with removing cleavage sites of CD154, like TNFα taught by Mueller et al., to achieve similar properties of stability and/or retard cleavage,

which, in turn, is consistent with the claimed molecules, ones with better resistance to cleavage than either native CD154 or TNFα.

The following of record is reiterated as it addresses applicant's arguments.

Applicant's arguments in conjunction with the Foon Declaration, filed 05/21/2007, as well as with the Prussak 132 Declaration, filed 10/05/2006, have been fully considered but have not been convincing essentially for the reasons of record.

In particular, applicant submits that the claimed molecules represent a particular combination of elements that one would not readily select from the range of variables suggested by the cited art and that the particular selection claimed, which resulted in near elimination, not just reduction, of soluble TNFα release could not have been predicted.

Further, applicant submits that Mueller et al. only suggests that removal of the disclosed portion of Domain III of the TNFα molecule will reduce release of soluble TNFα in certain cell types;
while evidence has been provided that the particular selection claimed resulted in near elimination, not just reduction of soluble TNFα release (see Foon Declaration).

Applicant further relies upon KSR Int'l Co. v. Teleflex, Inc., 550 US __, 2007 WL 123837, at 12 (2007), for the position that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (emphasis added).
Here, applicant submits that one could construct a wide range of different constructs following Kipps et al. (to obtain expression in expression-incompetent cell types), and might try to modify cleavage sites in the chimera (to enhance stability). If one did so, one might possibly hope that release of soluble TNFa could be reduced from molecules lacking a cleavage site from Domain III of the TNFa molecule and/or that the chimera might be expressible in otherwise expression-incompetent cell

As discussed during the interview, the cited references would not readily lead one of ordinary skill in the art to predict that soluble TNFa release could be eliminated from cells transfected with the claimed chimera in particular.

In corroboration of that conclusion applicant submits the Foon Declaration, which concludes:
Nothing in the references points one to select a CD154/TNFa chimera lacking a metalloproteinase site in particular, nor do the references offer a reasonable basis upon which to expect that cleavage from such a chimera would be abrogated to the same or greater degree than demonstrated by Mueller, et al. for the TNF molecule they tested. Even in view of the Kipps application's disclosure, one could not have predicted, a priori, the best combination of TNF family member segments to fuse to the domain IV of TNF to create a stabilized molecule.
See paragraph seven (7) of the Foon Declaration.

However, it is also noted that paragraph five (5) of the Foon Declaration acknowledges that Mueller did investigate the in vitro and in vivo biological activity of a "non-cleavable" transmembrane form of mouse TNF and did delete all the known cleavage sites from the murine molecule. Further, the Foon Declaration acknowledges that Mueller demonstrated that this functional TNF molecule was expressed for the most part in a membrane stabilized manner.

While applicant relies, in part, upon the Foon Declaration indication that the relative cleavage of the soluble TNF molecule was cell line dependent,
the claims are not limited to any particular cell line.

Therefore, applicant's arguments of unexpected results do not appear to be commensurate in scope with the claims, particularly in view of the motivation and expectation of success in constructing such chimeric TNF-CD40L molecules at the time the invention was made.

In addition and in response, in part, to paragraph six (6) of the Foon Declaration concerning that "nothing in the Mueller paper would cause one to suspect that removing a metalloproteinase cleavage site from the CD154 element of a TNFα chimera would produce even the same resistance to cleavage enjoyed by the TNF molecule tested by Mueller, the following is noted.

Kornbluth has been added to provide further motivation and expectation of success in modifying the proteinase cleavage site(s) in constructs comprising CD40L as well as TNF by teaching that CD40L containing protease-susceptible amino acid sequences, which can be eliminated by mutagenesis to retard the cleavage of CD40L from fusion proteins, which, in turn, would favor the local persistence of the CD40L stimulus (See entire document, particularly the Discussion of Example on pages 9-10 and paragraphs [0098] – [0099]).

Also, with respect to the teachings of Kornbluth,
the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., In re Kahn, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006 and In re Dillon, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991).

Here, generating chimeric molecules comprising CD40L and TNF was a simple modification of the cleavage site(s) from either the CD40L or TNF molecules or encoding molecules, wherein the prior art recognized the advantages of such modifications to increase the biological activity or the efficacy of the CD40L and TNF molecules.

With respect to motivation, expectation of success and predictability and the other rationales offered by the Supreme Court, the prior art modified CD40L and TNF molecules, including their integration into chimeric molecules for the very reasons as applicant to generate of derive chimeric molecules comprising CD40L and TNF without cleavage sites that would limit the effects of the chimeric molecule and, in turn, would have been expected to translate into the increased desired biological activity or efficacy of said molecules

In this regard, applicant's reliance on the asserted unpredictability that the particular claimed constructs does not detract from the clear teachings, motivation, expectation of success, predictability, design choices and market forces at the time the invention was made to address the nature of the problems associated with cleavage sites in CD40L and TNF by modifying said cleavage site(s) that limit the efficacy or desired biological activity of said molecules.

Although it is recognized that there may be some degree of unpredictability at the time the invention was made concerning the ability or the extent of the stability of stabilizing CD40L-TNF on different cell types,
the possibility or even observations of such does not compel a conclusion of non-obviousness herein.

Consistent with KSR, the operative question in this "functional approach" is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions."

The claim is to a structure already known in the prior art that is altered by the mere substitution of one known element for another element known in the field for the same function. The facts themselves show that there is no difference between the claimed subject matter and the prior art but for the combination itself. "[T]he mere existence of differences between the prior art and an invention does not establish the invention's nonobviousness. The gap between the prior art and respondent's system is simply not so great as to render the system nonobvious to one reasonably skilled in the art."
Dann v. Johnston, 425 U.S. 219, 230, 189 USPQ 257, 261 (1976)

The following of record with the addition of Kornbluth et al. addressed above is reiterated for applicant's convenience

Applicant's arguments, in conjunction with the Prussak 132 Declaration have been fully considered but have not been convincing essentially for the reasons of record.

In response to applicant's arguments that there is no or insufficient suggestion to combine the references to modify the prior art to render applicant's invention obviousness, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

While applicant in conjunction with the Prussak Declaration appear to focus on the lack of sufficient motivation and expectation of success on the modifications suggested by Mueller et al. (J. Biol. Chem.274: 1999).
it appears that such assertions appear to overstate the deficiencies of the prior teachings of Mueller et al., and more in particular, the teachings of the combined references.

In this case the teachings of the prior art references pertaining to the difficulties in preventing the deleterious effects of cleaved TNFα and, in turn, their teachings indicating success in generating chimeric accessory molecules to solve the same or similar problem would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144

As pointed out previously, both Kipps et al. (U.S. Patent No. 7,070,771 and WO 98/26061) (see entire documents) teach chimeric molecules, including nucleic acids encoding accessory molecules ligands (and associated vectors, including viral vectors and regulatory regions host cells such as tumor cells and antigen presenting cells and methods of producing the chimeric molecules) which are made up of various domains and sub-domains of molecules derived from the tumor necrosis factor molecules, which, in turn, contain unique properties which lead to the stabilization of their activities and greater usefulness in the treatment of diseases (see entire document, including Abstracts and Summary of the Inventions). The Detailed Description of the Invention these prior art references describe the very CD154 / CD40L domain structures to be utilized as well as TNFα itself as well as the Domain Structure of Tumor Necrosis Factor Family Molecules (e.g. see Table 1 on column 15 of U.S. Patent No. 7,070,771 and page 29 of WO 98/26061).

While the prior art Kipps et al. references contemplate chimeric accessory molecules comprising any domain, sub-domain and portions of the disclosed molecules, including CD154/CD40L and TNFα (e.g., see Detailed Description of the Inventions), these references do not set out the particular nucleic acid molecules comprising a Domain IV fragment of TNFα and the rest of the molecule comprising CD40L per se.

Also, as noted previously, these Kipps et al. references do note that the fourth domain (Domain IV) of the accessory molecule ligand gene(s) is called the distal extracellular domain and that the secondary structures of the accessory molecule(s) were deduced based upon CD40L and human TNF (e.g. see column 14-15, overlapping paragraph of U.S. Patent No. 7,070,771 and pages 27-28 of WO 98/26061).

Further, the disclosures of the co-inventors own prior art references are very similar if not the same as the instant disclosure of generating chimeric accessory molecules comprising any domain, sub-domain and portions of the disclosed molecules, including CD154/CD40L and TNFα (e.g., see Detailed Description of the Inventions) as the instant disclosure.

While applicant and the Prussak Declaration acknowledge the teachings of Mueller et al., applicant submits that this reference only teaches modifying the wild-type TNFα in certain respects, including that the deletion of the cleavage site alone as not being sufficient to substantially eliminate soluble TNF release.

However, such a limited reading of Mueller et al. itself is not readily apparent and not found convincing with respect to the principles as well as advantages and expected beneficial results that would have been produced by their combination.

Again, the prior art is the same or nearly the same as the instant disclosure with respect to generating the same types of chimeric accessory molecules with the same direction to combining different elements of CD154/CD40L and TNFα to achieve the same or similar advantages and benefits as applicant's disclosure as filed.

As noted previously, Mueller et al. teach the advantages and, in turn, constructs comprising transmembrane TNFα, which include deleting proteolytic cleavage sites of TNFα to prevent the deleterious effects of cleaved TNFα (see entire document, including Abstract, Introduction and Discussion). Mueller et al. also discusses the role of TNFα in association with CD154 / CD40L as well as the use of transmembrane TNFα therapeutically (see Discussion, including page 38117, columns 1-2).

While Mueller's mutants were not human, the combined teachings including the Kipps' references clearly provided for the use of human constructs, particularly in light of their utilities in the treatment of humans.

As indicated above, Kornbluth has been added to provide further motivation and expectation of success in modifying the proteinase cleavage site(s) in constructs comprising CD40L as well as TNF by teaching that CD40L containing protease-susceptible amino acid sequences, which can be eliminated by mutagenesis to retard the cleavage of CD40L from fusion proteins, which, in turn, would favor the local persistence of the CD40L stimulus (See entire document, particularly the Discussion of Example on pages 9-10 and paragraphs [0098] – [0099]).

Therefore, it would have been prima obvious to the ordinary artisan at the time the invention was made to construct nucleic acids encoding chimeric accessory molecules, including the construction of TNFα on the extracellular domain with domains of CD154 / CD40L in order to take advantage of the known uses of TNFα, but to avoid the deleterious effects of some or pleiotropic properties of TNFα, such as endotoxic shock, as taught by both Kipps et al. references and Mueller et al. Both Kipps et al. references clearly teach mixing and matching members of the TNF family and rely upon the predicted structures of TNFα and CD154/CD40L per se as a basis for their teachings of constructing chimeric accessory molecules. Nucleic acids comprising SEQ ID NO: 1 would have been an expected or intrinsic property of chimeric molecules comprising human TNFα linked to CD154/CD40L Domains I, II and III.

One of ordinary skill in the art at the time the invention was made would have been motivated to select an extracellular domain of TNFα with CD154/CD40L domains to achieve the use of TNFα and to avoid the deleterious effects of TNFα by constructing chimeric accessory molecules which contain unique properties which lead to the stabilization of their activities and greater usefulness in the treatment of diseases, as taught by the Kipps et al. references.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One cannot show non-obviousness by merely asserting that the references do not provide the sufficient elements of obviousness or by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

Applicant's assertions of unexpected results is acknowledged, however the prior art provided sufficient motivation and expectation of success in constructing chimeric accessory molecules, including the construction of TNFα on the extracellular domain with domains of CD154 / CD40L in order to take advantage of the known uses of TNFα, but to avoid the deleterious effects of some or pleiotropic properties of TNFα, such as endotoxic shock, which in turn, is the same asserted advantages relied upon by applicant in the current application. Therefore, the asserted advantages and unexpected results appear to the same or nearly the same as the instant application.

Applicant's arguments have not been found persuasive.

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 2-4, 8, 11-12, 27-29, 32-41, 68 and 76-79 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 66 and 68-75 of USSN 11/015,117.

Although the claims are not exactly the same, the instant and copending claims are drawn to nucleic acid molecules / constructs encoding chimeric CD40L(CD154)-TNF molecules and their corresponding vectors and host cells.

Therefore, the instant claims and copending claims can anticipate or render obvious one another.

However, it is noted that there may be or are differences in the election of species between the copending USSNs or that the claims in the different copending USSNs may involve patentably distinct elements.

Therefore, applicant is invited to clarify the distinction between the copending claims, as the claims differ in their recitation of sequences or TNF family ligands.

9. Claims 2-4, 8, 11-12, 27-29, 32-41, 68 and 76-79 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable
over claims 1-15 of U.S. Patent No. 7,070,771 and
over claims 1-17 of U.S. Patent No. 7,495,090.

Although the claims are not exactly the same, the instant and copending claims are drawn to nucleic acid molecules / constructs encoding chimeric CD40L(CD154)-TNF molecules and their corresponding vectors and host cells.

Therefore, the instant claims and copending claims can anticipate or render obvious one another.

Also, it is noted that terminal disclaimers have been filed in these U.S. Patents over the instant application.

10. Claims 2-4, 8, 11-12, 27-29, 32-41, 68 and 76-79 are directed to an invention not patentably distinct from
over claims 66 and 68-75 of commonly assigned USSN 11/015,117 and
over claims 1-15 of commonly assigned U.S. Patent No. 7,070,771.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No., discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/
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Art Unit 1644
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